

REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claim 7 has been amended by deleting “and for preventing the occurrence of new recurrent oral aphthous ulcers (ROAU) consisting of” and introducing “comprising” as originally filed.

Claim 13 is new and recites the feature of the treatment of ROAU, which comprises the reduction of new ulcer occurrence as supported in the description under C3 on page 7, lines 18-19 and in the Nolan reference (Annex 1) as stated by the Examiner on Page 2, last paragraph and Page 5, line 5 of her Communication.

Claims 7-13 are presently pending before the Examiner.

Claims Rejections – 35 USC 112, first paragraph.

The Examiner has rejected claims 7-12 because the specification, while being enabling for the treatment of recurrent oral aphthous ulcers and for reducing the occurrence of recurrent oral aphthous ulcers, does not reasonably provide enablement for the prevention of new recurrent oral aphthous ulcers. This rejection is traversed.

In order to overcome this rejection, Applicant has now amended claim 7 to delete the feature of “prevention” and by specifying that the treatment of the recurrent oral aphthous ulcers comprises the reduction of occurrence of new ulcers.

In view of the amendment of claim 7, which eliminates “prevention” from the scope of the currently presented claims, the rejection for non-enablement has been overcome and withdrawal of the § 112, first paragraph, rejection is solicited.

Claims Rejections -35 USC § 103

The Examiner has rejected claims 7-12 as being unpatentable under § 103(a) over Di Schiena (EP0444492) in view of Saxen et al. This rejection is traversed.

Applicant keenly disagrees with the Examiner's position and in support of the non-obviousness of the claimed invention hereby presents the following arguments.

The Examiner states that "Di Schiena teaches pharmaceutical compositions comprising 0.2 to 10% sodium hyaluronate having molecular weight between 800,000-4,000,000. Di Schiena does not exemplify the treatment of recurrent oral aphthous ulcers using the composition." [emphasis added]. Furthermore, the Examiner states that "Saxen et al. teach that recurrent aphthous ulcers are a common disorder..... A reduction in pain was observed 10 minutes after application with no significant difference between the three topical agents [see abstract]. Ulcers were smaller after treatment with HA [page 359, Table 1]". [emphasis added]

The Examiner thus concludes that "it would be obvious to one of ordinary skill in the art at the time the invention was made to use Di Schiena's composition for the treatment of recurrent aphthous ulcers".

Moreover, in responding to the previous arguments of Applicant, the Examiner states that "Applicant argues ... that HA alone was less effective for long-term pain relief than HA with diclofenac, and that no significant change in ulcer diameter was observed. This argument is not persuasive because ulcers were smaller after treatment with HA [table 1], and a "a highly significant overall treatment effect" was observed in all groups... Thus the skilled artisan would know that application of HA to ulcers reduced pain and reduced the size of the ulcers somewhat".

Applicant is astonished at reading that the invention is rejected in view of these definitely questionable grounds.

First of all, the Examiner arbitrarily isolated sentences from Saxen et al. in order to conveniently lead to the claimed invention. This is a clear case of hindsight reconstruction of the claimed invention.

As a matter of fact, Saxen et al. at pages 358-359 under “RESULTS” teach that:

“No significant change in ulcer diameter or clinical appearance of the ulcer was observed throughout of the trial... A highly significant treatment effect was observed ($p=0.01$) in which diclofenac/hyaluronan was significantly better than lidocaine alone at 2 through 6 hours after application. Neither lidocaine nor hyluronan were significantly different from baseline pain level at 1 through 8 hours after application”

Therefore, the sentence referring to “the reduction in pain observed 10 minutes after application with no significant difference between the three topical agents” is expressly and unambiguously referring to the moment immediately after the application of the tested compounds, with no statistical significance in the test. As a matter of fact the subsequent sentence in the abstract is “A 35% to 52% pain reduction ($p<0.01$) was reported 2 to 6 hours after the application of diclofenac in hyaluronan, while HYALURONAN GEL ALONE and viscous lidocaine FAILED to produce significant VAS reduction”. This is clear to the skilled artisan, who clearly knows that a result can only be said to be relevant in the treatment of an illness if the result is found to be significant after being subjected to statistical analysis. In a test lasting 8 hours the observation made after only 10 minutes cannot be deemed to be a significant result, the result being relevant and significant, conversely, only at the end of the test after a statistical analysis.

Therefore, even if in the first 10 minutes the three groups were approximately similar in their results, after 2 hours (out of 8!!!) it is apparent that the group receiving diclofenac /hyaluronan was much better than the group receiving HA alone as can be seen from Table II.

The same can be repeated for the sizes of the ulcers. As a matter of fact, according to the article under the RESULTS paragraph “No significant change in ulcer diameter or clinical appearance of the ulcer was observed throughout the trial” and “the demographic characteristics of the treatment groups are shown in Table I”. Therefore, there is no result reported in Table I as affirmed by the Examiner, but only the demographic characteristics of the treatment groups, and the only teaching reported in the article is “the highly significant difference between diclofenac in hyaluronan and hyluronan 1 to 8 hours after application” (page 360, lines 35-37).

This is also confirmed by the conclusion under the RESULTS title, wherein it is stated:

“The **blunting action of hyaluronan**, an agent with no known analgesic or anesthetic activity is probably due to the coating action over the ulcer. **Hyaluronan is highly viscous, imbibes water and adheres to inflamed tissue.**

Carboxymethylcellulose, an INERT, viscous substance also forms a coating over the ulcer ... In light of these properties, one can postulate that protective layering of the ulcer was a significant component of the overall treatment effect.. This is consistent with trials evaluationg hydroxypropylcellulose, a similar, PHARMACOLOGICALLY INERT agent that was shown to be effective in reducing aphthous ulcer pain”.

Therefore, the results in reducing pain after only 10 minutes was meant as a result of a PHARMACOLOGICALLY INERT component in the treatment, but having the capability of being viscous and, therefore, being protective. Indeed, **one of ordinary skill in the art would never have misinterpreted this prior art document as surprisingly has been done by the Examiner.** No therapeutic effect was associated with hyluronan alone, but only the protective action as to carboxymethylcellulose and hydroxypropylcellulose, which are inert viscous substances.

Thus, a skilled person reading this document would **no doubt be aware of the fact that Saxen et al. only refer to the therapeutic action of diclofenac in hyaluronan**

in the treatment of recurrent aphthous ulcers and that "HYALURONAN GEL ALONE and viscous lidocaine FAILED to produce significant VAS reduction" .

From the above essential features, it is evident that the skilled person is taught to use diclofenac as the only available treatment in recurrent aphthous ulcers.

Now, Applicant wonders how the skilled person would be motivated to modify the teaching of Saxen et al. in the direction of the claimed invention, thus combining with the Di Schiena product, when all of the conclusions in reducing the pain in recurrent aphthous ulcers by Saxen et al. teach away from the sole use of hyaluronan.

In this regard, how can the Examiner state that "it would be obvious to one of ordinary skill in the art at the time the invention was made to use Di Schiena's composition for the treatment of recurrent aphthous ulcers", without acknowledging that this is an evident hindsight reconstruction?

It is clear that the expectations of success indeed fall flat when the teaching of Saxen et al. is not followed, i.e. when diclofenac is not used in the treatment. Thus, how could the skilled person, at the time the invention was made, believe he or she would possibly succeed in treating ROAU without using diclofenac? More importantly, how could he/she expect to reduce the number of ulcers already formed or the sizes thereof in view of Saxen et al. that teach that no significant change in ulcer diameter or clinical appearance of the ulcer was observed throughout of the trial?

Applicant, therefore, wonders why the skilled person would have even contemplated combining Saxen et al. with Di Schiena , when the latter clearly does not pertain to the field of endeavour of the invention, since it is not pertinent to such a specific pathology as ROAU.

And also, even arbitrarily decontextualizing the information as the Examiner has done with Di Schiena, thus considering ROAU as a common pathology of inflammatory afflictions of the oral cavity in order to combine Di Schiena with Saxen

et al., the question remains why would the skilled person not have used diclofenac with hyaluronic acid as clearly suggested by the results of Saxen et al. in treating ROAU?

Applicant is definitely convinced that the Examiner came to her conclusions on the basis of a further hindsight, while it is clear that the skilled person would have had no reason to combine Di Schiena with Saxen et al. in order to achieve the claimed invention.

In the Experiment described in Annex 1, filed with the September 26, 2008 Response, Applicant achieved the following results:

- (a) a statistically significant ($p=0.04$) reduction of ulcers on day 5 in patients treated with HA(1.65 ± 0.25) when compared to the placebo group (2.4 ± 0.26) (see table 2)
- (b) a statistically significant ($p=0.047$), reduction on day 4 of **new ulcer occurrence** in patients treated with HA(2) when compared to the placebo group (10) (see table 4)
- (c) a statistically significant ($P<0.001$) increase of patients free from ulcers on day 7 in patients treated with HA (24) when compared with patients treated with placebo (19) see table 3.

This confirms without any doubt that the sole active ingredient hyaluronic acid in accordance with claim 7 can be used in the treatment of ROAU and this is a definitely unexpected result achieved by the claimed invention, particularly in view of Saxen et al.

For all the above reasons, Applicant is convinced that the invention as set forth in the currently amended claims is non-obvious and distinguishes over the prior art applied by the Examiner.

Accordingly, the rejection under § 103(a) has been overcome and should be withdrawn since the “preponderance of the evidence”, which is the standard to be

employed, establishes quite clearly the failure of the Examiner to establish a case of *prima facie* obviousness.

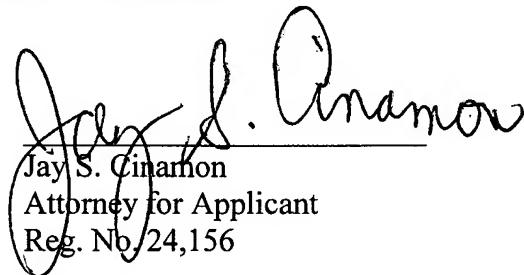
The issuance of a Notice of Allowance is solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

ABELMAN, FRAYNE & SCHWAB
Attorneys for Applicant

By


Jay S. Cynamon
Attorney for Applicant
Reg. No. 24,156

666 Third Avenue
New York, NY 10017-5621
Tel.: (212) 949-9022
Fax: (212) 949-9190